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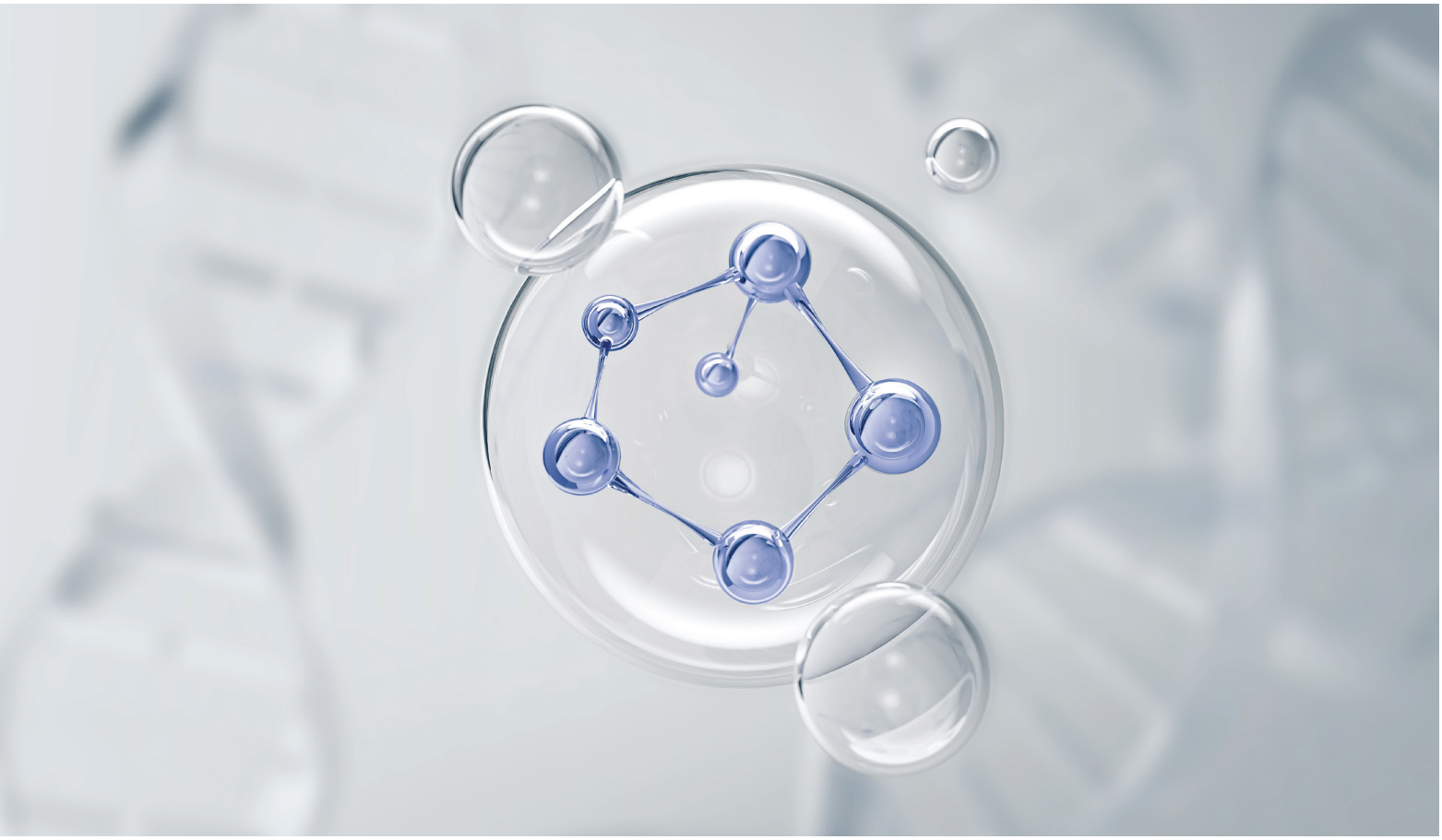

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WHITEPAPER

Small molecule orphan drugs: Balancing financial incentives and complex challenges

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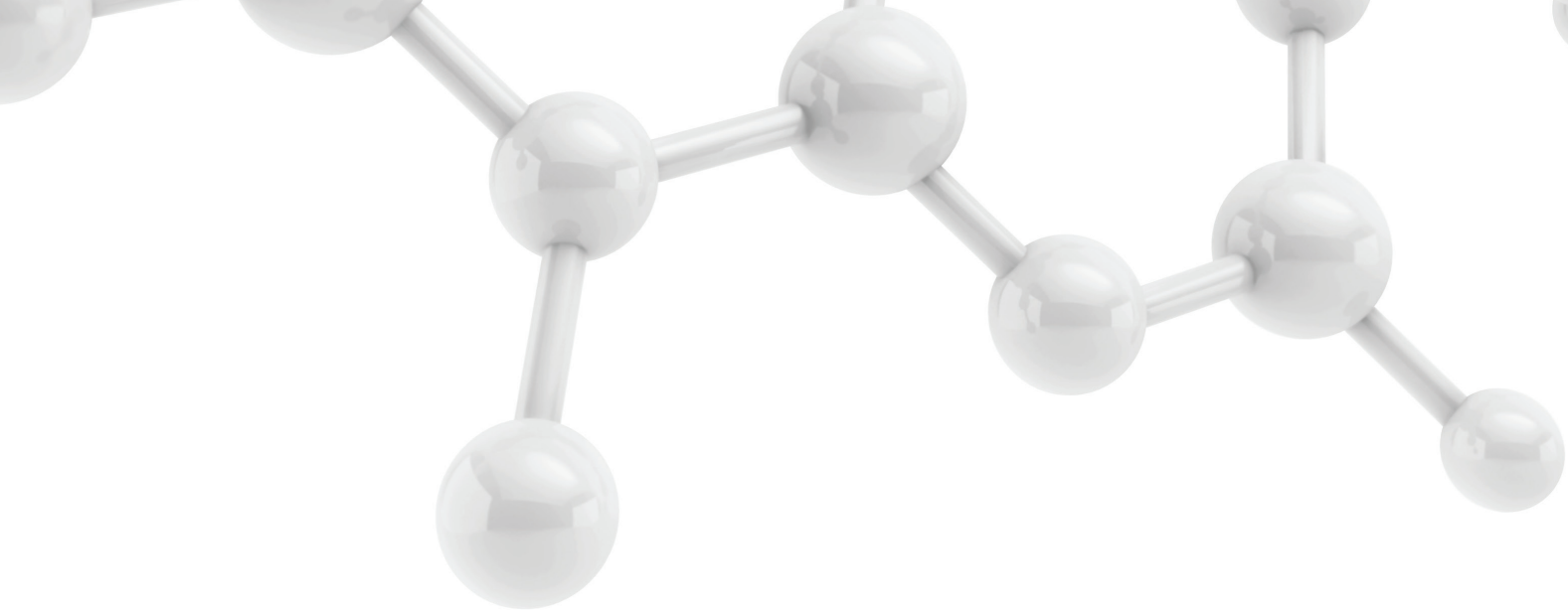


Abstract

The orphan drug industry focuses on developing life-changing and potentially life-saving treatments for patients living with rare diseases. Previously, the needs of these patients often went unmet because of the prohibitively high costs of developing drugs for small populations. The Orphan Drug Act of 1983 ushered in an era of incentives, government support, and regulatory agency assistance, making the development of drugs for rare diseases finan-cially feasible and changing the pharmaceutical landscape significantly. Nearly half of all drugs approved by the FDA in 2019 were orphan drugs, and the market value of this industry segment is anticipated to be $262 billion by 2024[1].

Achieving clinical and commercial success with orphan drugs requires overcoming numerous development and manufacturing challenges related to fast-tracked timelines, active pharmaceutical ingredient (API) supply lines, form-ulation scale-up, clinical trial establishment, and regional variation in legislation and regulatory policies. Meeting these challenges requires specialized skills, resources, and infrastructure, as well as agile supply chain manage-ment with the flexibility to accommodate commercial needs.

This whitepaper offers a roadmap for navigating the complexities of orphan drug development based on the following key features.

- close alignment of clinical and CMC teams
- a continuous regulatory feedback loop
- predictive API modeling
- a robust formulation development program
- an integrated, single-vendor strategy

Changing the lives of patients living with rare diseases requires collaboration, communication, and careful planning that incorporates regulatory, clinical, scientific, and commercial strategy. It also requires a commitment to advancing science to speed solutions.

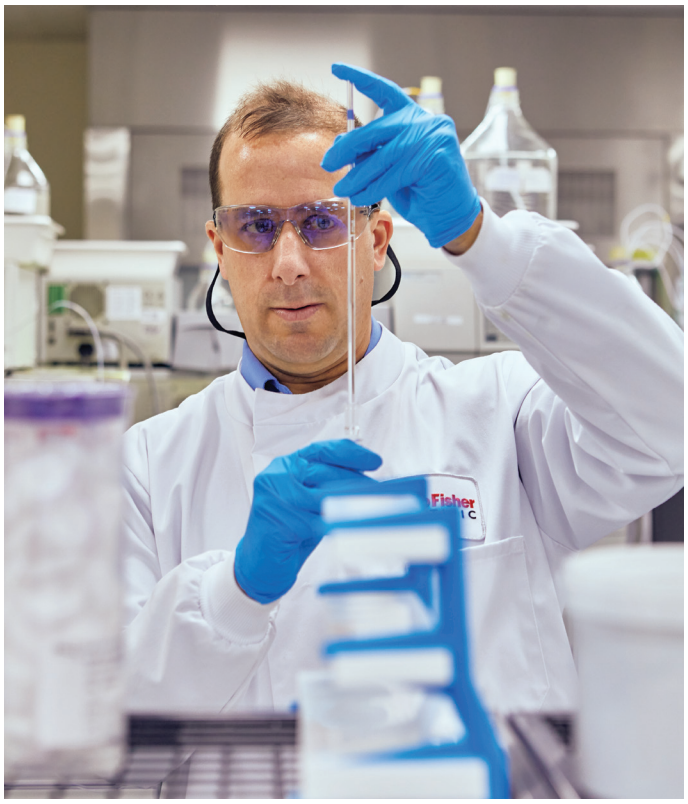
Introduction

The Orphan Drug Act (1983) was enacted to stimulate the development of drugs for rare diseases affecting small patient populations. The legislation provided financial incentives that included the waiver of FDA fees, market exclusivity for approved orphan drugs, tax incentives, and public diffusion of orphan innovation.[1] Since its passage, more than 7,400 orphan drug designation requests have been submitted and nearly 600 orphan drugs have been approved[2,3].

Even with some of the financial and logistical barriers removed, designing orphan drug formulations for oral solid dose (OSD) presents several challenges related to the complexity of the substances, the need for novel and sophisticated synthetic routes and production methods, and accelerated timelines for getting these products to market. Specifically, sponsors face the difficulty of scaling up early-phase formulations for process validation, establishing clinical trials for small patient populations, managing geographically dispersed trial participants, and navigating complex regulatory environments of multiple countries. These obstacles can be overcome through careful planning and stakeholder collaboration, beginning with close alignment of clinical and chemistry, manufacturing, and control (CMC) teams.

Aligning clinical and CMC teams

Speed to approval of orphan drugs relies on accelerated clinical studies. However, with fewer patients involved in the early and later phases for orphan drugs than with traditional drug products, the result is relatively smaller batch sizes. Simple, phase-appropriate formulations are frequently used at this stage, but these are usually not scalable or suitable for process validation. These factors create challenges between the clinical team moving as quickly as possible and the CMC team that must stay ahead and anticipate potential risks in scale-up. Robust coordination between these groups can help sponsors meet deadlines for clinical trial material (CTM) supply.



Unlike sterile drug products, where the difference between a Phase I and Phase III formulation might be more vials per batch, OSD forms are more complex and present additional CMC challenges. OSDs frequently change during clinical development due to patient requirements, release profile, or solubility issues. Moreover, formulation scale-up is heavily dependent on the physical properties of the drug substance, which can change when shifting from reaction vessels to support larger-scale synthesis of API.

Because CMC requirements often become critical path tasks on the submission timeline, CMC requirements should be initiated early and be aligned with the various clinical development phases throughout the program. This helps avoid pauses between activities that idles your staff and facility while overhead costs run unabated.

Shortening timelines and enabling early development and scale-up

Many sponsors preparing for first-in-human (FIH) trials can get distracted by the market image of their product before they've demonstrated safety and tolerability. This can be a bigger temptation with the accelerated timelines of orphan programs. Getting to FIH trials quickly will be for naught if doing so compromises quality, safety, or efficacy, or if it impedes later-phase progress.

Integrated lab-to-clinic drug development solutions can help sponsors optimize the speed/risk balance. For example, Thermo Fisher Scientific's Quick to Clinic™ program, sponsors can begin FIH trials with a fit-for-purpose formulation (e.g., API in a capsule) while starting pre-formulation and formulation development activities during Phase I. Sponsor teams can realize significant timeline savings when they collaborate on near-concurrent API, drug product, and clinical activities to pull forward CMC activities in an orphan program (as Figure 1 illustrates).

This approach does require earlier investment to develop scalable formulations, leading to increased risk for both API and drug product activities; however, having a plan in place with API in hand and product prototypes available for the final formulation will allow sponsors to move quickly. More importantly, CMC data needed for the regulatory dossier are available.

Navigating a complex regulatory environment

Orphan designation or not, a complete CMC package is required for approval of a new drug. Non-orphan development programs will involve multiple batches and scale changes for API and drug product over the six to ten years it may take on the path to an NDA. Orphan trials have fewer patients, so there are smaller batches and fewer manufacturing runs to generate development history, such as process experience and stability data, that is needed to support the validation section of the CMC dossier. Before clinical trials start, sponsors should meet with regulatory authorities to present their clinical strategy and describe how the CMC program will support it. Feedback from the agency will guide clinical milestones, the API and drug product strategies that the clinic, and the CMC data for the registration batches for NDA submission.

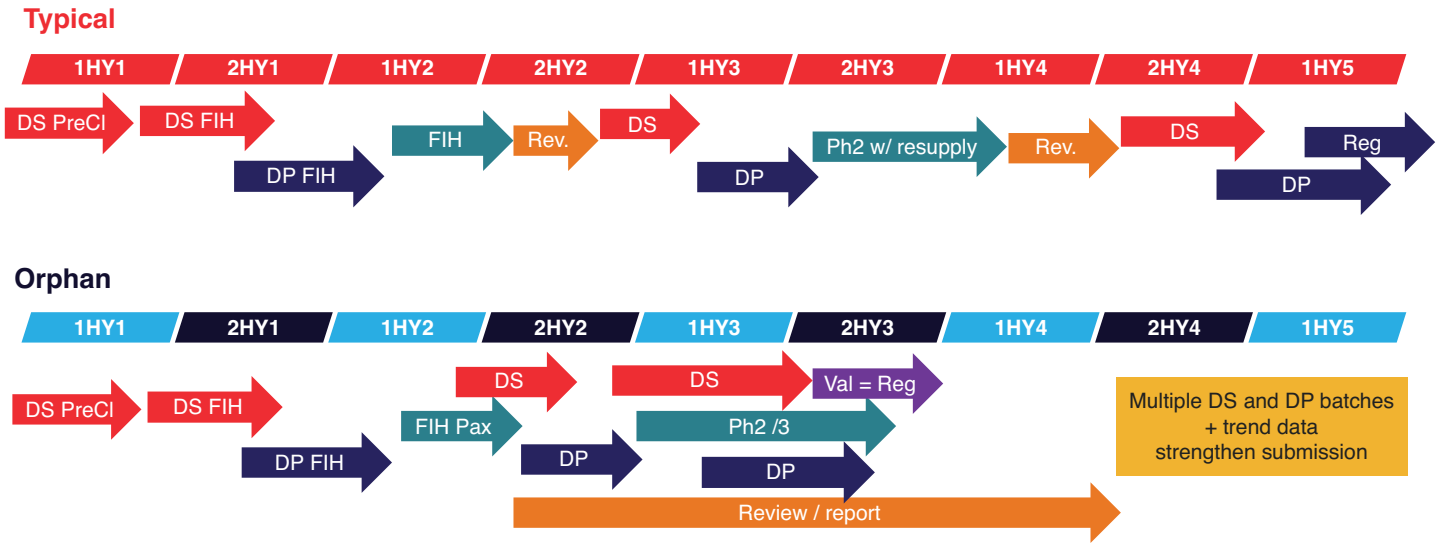


Figure 1: Pulling forward the CMC activities for orphan products to enable faster clinical supply for trials

Regulatory feedback on a sponsor's strategy is invaluable to increasing chances of approval. The FDA may accept more risk for a first-in-class breakthrough therapy — potentially resulting in faster approval with less data — but the agency will want to understand the benefits and risks to the patients and how quality will be maintained through development. While a complete package is expected, sponsors may be permitted to generate data on a rolling basis and include it in clinical reviews as each phase completes. The agency may agree to post-approval commitments in terms of updates to the CMC package. For example, the registration batches could also be the three validation batches conducted over time.

Accelerating development with predictive API modeling

Predictive and analytical tools de-risk early CMC programs for smarter scale-up. For example, computational modeling programs can assess an API's risk for poor solubility and predict technologies and potential formulations to solu-bilize the API. This analysis can be done before a candidate has been nominated, leading to greater success in IND-enabling studies. Additionally, compaction simulation and powder flow rheometry supports smarter formulation development by characterizing API and blends/granules, and predictive stability quickly identifies those stable formulations and packaging configurations to carry forward into scale-up.

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Building a robust formulation development strategy

Early and careful investment in development will yield strong dividends later in API development and, subsequently, product development. Efforts that can prevent problematic impurities that can cause issues later include closely reviewing the API synthetic pathway to enable smart selection of regulatory starting materials; avoiding intermediates with genotoxicity potential; and avoiding any other potentially hazardous reagents. Especially important for preclinical and Phase I stages is the purity profile of an API, which will change in subsequent batches and during synthetic optimization. A target purity of 98% is appropriate.

Leveraging convergence syntheses and scalable chemistries and fully characterizing every batch can enable smarter formulation development. Because orphan drug programs move quickly, it is essential to document all process improvements in API synthesis as well as effects on formulation and performance. Regulatory submissions should be updated accordingly with scientific rationale for any changes. This is especially important when alterations demonstrate a better benefit-to-risk ratio for patients.

While it may be tempting to manufacture as few batches as possible, doing so introduces unnecessary risk. Repeated API manufacture provides data on process, physiochemical properties, and impurity/stability profiles that can highlight potential issues later. Additionally, data on multiple API batches as part of a continuous and adaptive strategy provides a foundation for a continuous validation strategy that will support the move toward scale-up and commercialization. More product batches means more valuable data for developing control strategies needed for process validation and a detailed CMC section for the NDA.

Adopting an integrated, single-vendor strategy

For most pharmaceutical companies, outsourcing components of the orphan drug development process is part of the core strategy because of the unique challenges associated with these compounds. One of the most important and potentially underappreciated question sponsors should consider with respect to outsourcing is whether to contract with multiple vendors for different activities along the development and manufacturing pathway or whether to work with a single vendor with integrated capabilities.

Answering that question requires first determining which vendors can provide access to the scientific and process innovations needed to develop drug molecules as efficiently as possible and which have the manufacturing agility to flex and adapt to product and volume changes through each phase of development. Certainly, cost is a consideration, but it is not an indicator of value on its own.

For example, working with multiple vendors may seem appealing from a cost perspective, but it can present significant challenges to timeline management, which in turn impacts cost. Communication across multiple CDMOs can be difficult to manage and coordinate, especially when processes don't naturally align. This might be the case when a drug product vendor doesn't begin activities until the drug substance has been received from another vendor. Unexpected and uncommunicated changes to shipment/receipt dates can cause confusion and costly delays, and geographic and regional differences can introduce unplanned logistical challenges related to languages, time zones, and regulatory guidelines.

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Working with a single, integrated vendor who can manage all of the above challenges might incur additional upfront costs, but the value can be recouped through full alignment of inter-site activities and smoother program execution, often directed by a single program manager. Such was the experience of a pharmaceutical company that reached out to Thermo Fisher for drug product development and supply for its orphan drug. A consultant for the same company connected with an API request. Thermo Fisher subject matter experts (SMEs) reviewed the separate requests and quickly notified the customer that the API request was insufficient and could delay their target clinical start. The SMEs offered a solution: An integrated program with aligned API and product timelines that ensured sufficient supply, early start on formulation using R&D API, and clinical packaging, labeling, and supply to support the multi-site trial. A single program manager oversaw and coordinated the work of the site project managers. The integrated approach expedited the development timeline by 11 weeks, improving competitive positioning and reducing overall costs.

Conclusion

Of the more than 7,000 rare diseases that have been identified, only 5% have treatments, according to the National Institutes of Health[4]. In addition to the potential market opportunity, these values point to tremendous opportunity to change the lives of the millions of people living with rare diseases globally. Doing so requires overcoming some of the inherent difficulties associated with rare disease research and orphan drug development, including low disease prevalence, disease severity, small patient populations, and difficulty of patient recruitment.

The nature of orphan drugs also introduces manufacturing challenges. The drug substances themselves can be highly complex and often require specialized routes and production methods, and the low volume/high value production requirements can challenge the economics of manufacturing.

For companies pursuing an orphan drug, successfully traversing the path to regulatory submission requires striking the right balance of speed-to-clinic and cost. While there is no one-size-fits-all approach, shared characteristics of successful development projects include early and frequent engagement with regulatory authorities, alignment of CMC and clinical activities, transparent communication among internal and external stakeholders, and an integrated vendor strategy.

References

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About us

Thermo Fisher Scientific provides industry-leading pharma services solutions for drug development, clinical trial logistics and commercial manufacturing to customers through our Patheon brand. With more than 65 locations around the world, we provide integrated, end-to-end capabilities across all phases of development, including API, biologics, viral vectors, cGMP plasmids, formulation, clinical trials solutions, logistics services and commercial manufacturing and packaging. Built on a reputation for scientific and technical excellence, we provide pharma and biotech companies of all sizes instant access to a global network of facilities and experts across the Americas, Europe, Asia and Australia. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to Care™ program. Our Quick to Clinic™ programs for large and small molecules help you balance speed and risk during early development so you can file your IND quickly and successfully. Digital innovations such as our mysupply Platform and Pharma 4.0 enablement offer real-time data and a streamlined experience. Together with our customers, we're rapidly turning pharmaceutical possibilities into realities.

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Kevin provides technical consulting for drug delivery, early formulation development programs, and scale-up. He focuses on finding solutions that align with a client's clinical study design for small molecules with biopharmaceutic and physicochemical challenges. Kevin brings more than 25 years of industrial experience in synthesis, formulation and solubilization technologies (oral and sterile), and adaptive clinical studies, having worked as an independent consultant and as a scientist at various CDMOs in addition to his 9 years at Thermo Fisher Scientific's Pharma Services business. Kevin has a PhD Inorganic Chemistry (Ohio University), MS Polymer Chemistry and BS Chemistry (Texas State University).

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